R_6-R_9 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3; and

R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl,

with the proviso that the H^+, K^+-ATPase inhibitor is not pantoprazole.

REMARKS

I. Claim Amendments

The independent method claims 1, 18, 26 and 27 have been amended to clarify the transition between the preamble and the body of the claim. Applicants submit that the recitation of the phrase "which comprises" provides a clear separation between the preamble and the body of the claim. Therefore, the claimed invention is defined by those features which come after the transition phrase "which comprises" and which are recited in the body of the claim. These features include the recitation "wherein the method induces an extended blood plasma profile of the H^+, K^+-ATPase inhibitor".

Although independent formulation claims 7 and 19 have not been amended, the same argument applies to claims 7 and 19 which include the transition phrase "comprising". Accordingly, the recitation "wherein the formulation induces an extended blood plasma profile

of the H^+, K^+-ATPase inhibitor" does not appear in the preamble since the recitation of that feature comes after the transition phrase "comprising".

No new matter has been introduced by any of the claim amendments.

II. Claim Rejection – 35 U.S.C. §103

The Office Action provides that claims 1-11, 15, 16, 18-21 and 23-25 remain rejected under 35 U.S.C. §103 in view of US 5,330,982 to Tyers ("Tyers") for the reasons of record. Applicants wish to remind the Examiner that claims 20, 21, 23-25 were cancelled and that claims 26 and 27 were added. Therefore, the pending claims are claims 1-11, 18, 19, 26 and 27 as correctly indicated on page 1 of the Office Action.

Tyers is directed to a combination therapy comprising a 5-HT receptor antagonist and a H^+, K^+-ATPase inhibitor. The Examiner alleges that Tyers discloses an extended release formulation comprising the two active ingredients which would result in an extended plasma profile of the actives.

Applicants respectfully disagree. Applicants submit that Tyers does not disclose an ***extended release*** formulation as alleged by the Examiner. Rather, it is submitted that Tyers discloses a ***controlled release*** of either the 5-HT receptor antagonist or the H^+, K^+-ATPase inhibitor or both ingredients (col. 10, lines 53-55):

> Preparations for oral administration may be suitably formulated to give ***controlled release*** of one or both active ingredients (Emphasis added).

The expression "controlled release", as used by Tyers, is understood to mean a conventional tablet formulation known in the art. For example, Tyers discloses the following at column 11, lines 53-55:

> The tablets may be coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques.

It is known in the industry that hydroxypropyl methylcellulose is a conventional tablet coating material which is used to obtain a smooth tablet surface. Thus, there is no suggestion of a formulation providing an extended release.

Furthermore, the direct compression tablets and wet granulations tablets illustrated in the examples appearing in columns 11 and 12 of Tyers are prepared without any film or coating that would provided an extended release. In fact, the examples provide no suggestion that the tablets comprising omeprazole, i.e., an acid-labile substance, should contain an enteric coating which does not dissolve in the acid environment of the stomach but releases the drug when the enteric coat dissolves in the alkaline environment of the small intestines. Notwithstanding the failure of Tyers to disclose or suggest an enteric coating layer, the person of ordinary skill in the art would know that an enteric coating layer is necessary to protect the H+, K+-ATPase inhibitor from the acidic environment of the stomach.

At best, therefore, Tyers discloses a conventional tablet formulations giving a controlled release, e.g., an enteric coated formulation. As such, Tyers does not suggest the claimed method to induce an extended blood plasma level of the H^+, K^+-ATPase inhibitor.

Moreover, the earliest filing date of Tyers, i.e., the priority date, is December 17, ***1986***. As of the priority date of Tyers, it was common knowledge that the plasma half-life of a proton pump inhibitor, e.g., omeprazole, is 0.5-1 hour whereas the duration of acid inhibition is considerably much longer, i.e., 3-4 days (Lind et al., Gut, 24:270-276 (***1983***). The Examiner's attention is also directed to Martindale: The Extra Pharmacopoeia 13th Ed. (***1993***) ("Martindale") which was cited by the Examiner in support of the §102 rejection of record. The following disclosure appears in the left-hand column of page 897 of Martindale:

Absorpti n and Fate

Following absorption, omeprazole is almost completely metabolized in the liver and rapidly eliminated, mostly in the urine. ***Although the elimination half-life from plasma is short, its duration of action with regard to inhibition of acid secretion is much longer allowing it to be used in single daily doses***...(Emphasis added)

This lack of temporal relationship between the plasma concentration of omeprazole and the degree of acid inhibition is due to the long-lasting binding activity of the active inhibitor to the gastric pump (See, specification at page 2, lines 16-20). Accordingly, in 1986 when Tyers was first filed, there was no apparent need and certainly no motivation to prepare a formulation to give an extended plasma profile of the proton pump inhibitor. The person of ordinary skill in the art would have dismissed and rejected the pharmacological need to extend the plasma profile of the proton pump inhibitor in view of the known long-lasting binding effect of the proton pump inhibitor as reported by Lind et al. It is no surprise, therefore, that there was no known formulation or method of treatment to extend the plasma profile of a proton pump inhibitor in 1986 when Tyers was first filed.

In summary, therefore:

1. At best, Tyers discloses a conventional tablet formulation, e.g., an enteric coated formulation, giving a controlled release of one or both of the active ingredients;
2. As of the priority date of Tyers, i.e., December 17, 1986, it was known that the duration of acid inhibition (3-4 days) of proton pump inhibitors was considerably longer than the actual plasma level (0.5-1 hour) of the inhibitor; and
3. As of the priority date of Tyers, i.e., December 17, 1986, there was no need to prepare a formulation to give an extended plasma profile of the proton pump

inhibitor in view of the known long-lasting binding effect of the proton pump inhibitor as reported by Lind et al.

In conclusion, therefore, Tyers neither suggests nor provides the requisite motivation to do what Applicants have done. Applicants' invention represents a pioneer discovery and an unconventional method of treatment for improving the inhibition of gastric acid secretion by inducing an extended blood plasma profile of the H^+, K^+-ATPase inhibitor.

For all of the foregoing reasons, withdrawal of the §103 rejection in view of Tyers is requested.

III. Claim Rejection – 35 U.S.C. §102

The Office Action provides that 1-11, 15, 16, 18-21 and 23-25 are rejected under 35 U.S.C. §102(b) or §102(e) in view of WO 96/01624. Applicants wish to remind the Examiner that claims 20, 21, 23-25 were cancelled and that claims 26 and 27 were added. Therefore, the pending claims are claims 1-11, 18, 19, 26 and 27 as correctly indicated on page 1 of the Office Action.

The Examiner alleges that WO 96/01624 discloses the same compounds as the claimed invention. Moreover, the Examiner states that the recitation "inducing an extended blood plasma profile", as recited in the independent claims, has not been given any patentable weight because it appears in the preamble.

For the reasons given in Section I, above, Applicants respectfully and strongly disagree with the Examiner's position that the recitation "wherein the method [or formulation] induces an

extended blood plasma profile" appears in the preamble. The expression clearly comes after the transitional phrase "comprising" or "which comprises" which separates the preamble from the body of the claim. Therefore, the expression "wherein the method [or formulation] induces an extended blood plasma profile" appears in the body of the claim and must be given patentable weight as a feature defining the claimed invention.

Furthermore, the Examiner's statement that the compounds of the cited WO 96/01624 are the same as the claimed invention is inconsistent with the prosecution history. The cited WO 96/01624 is the PCT publication of PCT/SE95/00678 which was filed as a U.S. national stage application and eventually matured as US 5,753,265 to Bergstrand et al. (the "'265 patent"). The claimed invention was previously rejected under 35 U.S.C. §102(e) in view of the '265 patent, but this rejection was withdrawn as noted on page 2 of the Office Action (Paper No. 22), mailed September 13, 2001. Moreover, the Interview Summary (Form PTOL-413) of the interview which occurred on April 10, 2001 provides that the §102 rejections based on the '265 patent, as well as on US 5,817,338 to Bergstrand et al. (the '338 patent"), would be dropped since the claimed invention is not disclosed by the '265 and '338 patents.

Therefore, Applicants submit that the rejection based on WO 96/01624 should be withdrawn for the reasons of record that the rejection based on the '265 patent was withdrawn. Furthermore, WO 96/01624 does not disclose or suggest the claimed method of treatment and claimed formulation wherein the method and formulation induce an extended blood plasma profile of the H^+, K^+-ATPase inhibitor. Thus, WO 96/01624 fails as an anticipatory reference since it does not disclose each and every feature of the claimed invention.

Withdrawal of the §102 rejection in view of WO 96/01624 is requested.

IV. Claim Rejection – 35 U.S.C. §102

The Office Action provides that 1-11, 15, 16, 18-21 and 23-25 are rejected under 35 U.S.C. §102(b) in view of Martindale: The Extra Pharmacopoeia 13th Ed. (1993) ("Martindale"). Applicants wish to remind the Examiner that claims 20, 21, 23-25 were cancelled and that claims 26 and 27 were added. Therefore, the pending claims are claims 1-11, 18, 19, 26 and 27 as correctly indicated on page 1 of the Office Action.

The Examiner relies on the specific disclosure appearing in the middle column on page 897 of Martindale which provides that doses above 80 mg should be divided and given twice daily to patients with Zollinger-Ellison syndrome. Applicants submit that the Examiner is engaging in impermissible hindsight by citing this single statement out of context.

It is true that the treatment of Zollinger-Ellison syndrome may require the administration of high dosages of omeprazole. Specifically, as noted by Martindale, the initial recommended dosage is 60 mg once daily. However, in exceptional cases requiring a higher dosage, Martindale provides that doses above 80mg should be divided. Applicants submit that the Examiner is required to consider the prior effect of this exception in context of the preceding disclosure which appears in the left-hand column of page 897:

> **Absorption and Fate**
>
> Following absorption, omeprazole is almost completely metabolised in the liver and rapidly eliminated, mostly in the urine. ***Although the elimination half-life from plasma is short, its duration of action with regard to inhibition of acid secretion is much longer allowing it to be used in single daily doses***...(Emphasis added)

Thus, Martindale accurately describes the state of the art as it existed at the time the claimed invention was made. As disclosed on page 2, lines 16-20, of the specification, it was known that the duration of acid inhibition of one proton pump inhibitor, e.g., omeprazole, is 3-4 days despite a plasma half-life of only 0.5-1 hour (Lind et al., Gut 1983; 24:270-276). Notwithstanding a short plasma half-life, the duration of action is much longer.

Therefore, at the time the claimed invention was made, the prolonged duration of acid inhibition as noted by the prior art, including Martindale, would have dictated against the administration of an extended release formulation of H^+, K^+-ATPase inhibitor. Specifically, in view of a duration of relief lasting 3-4 days, an extend release formulation of an H^+, K^+-ATPase inhibitor was seemingly unnecessary.

The Examiner's attention is directed to the Example and Figure of the subject application. As described in the Example at pages 10-11, the pharmacological effect of the claimed invention was compared with a typical administration regimen involving omeprazole. Pursuant to the invention, a first group of subjects received 20 mg of omeprazole twice daily with 3 hours apart from each administration. A second group of subjects received a single 40 mg daily dose of omeprazole. With each group of subjects, the efficacy of the respective administration regimen in controlling acid secretion was measured. As shown in the Figure, the therapeutic effect of omeprazole is maximized, particularly on day 1, when the blood plasma concentration of the drug is extended by repeated single doses of omeprazole which are administered with 3 hours apart from each administration.

Applicants submit that the substantial improvement in efficacy as shown in Figure 1 is evidence of a patentable discovery. In view of the prolonged degree and duration of acid inhibition, it was indeed unexpected that the claimed invention would provide an extended blood

plasma profile of the H^+,K^+-ATPase inhibitor. Martindale does not disclose this feature either expressly or inherently. Instead, Martindale discloses the customary once daily administration of omeprazole:

> **Uses and Administration**
>
> The usual dose for healing of reflux oespophagitis is 20 40 mg ***once daily*** for 4 to 8 weeks; thereafter maintenance therapy can be continued with 20 mg ***once daily***....In the management of peptic ulcers a ***single daily dose*** of 20 mg, or 40 mg in sever cases, is recommended (Emphasis added).

The disclosure regarding the administration of high dosages of omeprazole, e.g., doses above 80 mg, to Zollinger-Ellison patients by dividing the dose represents an exceptional case to the recommended single daily dose. Therefore, the limited disclosure relied upon by the Examiner does not provide an enabling disclosure of the claimed invention. As such, Martindale does not properly qualify as an anticipatory reference. Moreover, the Examiner's reliance on this limited disclosure out of context is strongly suggestive that the Examiner may be using impermissible "hindsight", which is prohibited.

The Examiner also cites US 5,888,535 to Gray ("Gray") but does not rely upon Gray in support of a claim rejection. The Examiner states that Gray teaches the use of pantoprazole as an H^+,K^+-ATPase inhibitor which is useful in the inhibition of gastric acid secretion and the treatment of Zollinger-Ellison syndrome. Applicants submit that Gray discloses a method of treatment which is consistent with the typical administration of pharmaceuticals.

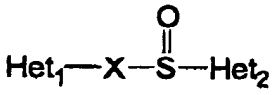
It warrants repeating - the pharmacological effect of a proton pump inhibitor is not dependent on the plasma concentration of the drug itself. This fact is confirmed by the prior art cited by the Examiner, i.e., Martindale. The prolonged degree and duration of acid suppression would dictate against the need for consecutive administrations of omeprazole.

Accordingly, Applicants' claimed invention represents a divergence from the typical use of H^+, K^+-ATPase inhibitors in the treatment of gastrointestinal disorders. It is Applicants' discovery that the unprecedented method of treatment and formulation inducing an extended blood plasma profile of the H^+, K^+-ATPase inhibitor had an unexpected improvement in the inhibition of gastric acid secretion.

Withdrawal of the §102 rejection in view of Martindale is requested.

Mark-up copy of amended claims 1, 18, 26 and 27 showing inserti ns and deleti ns:

1. (Four times amended) A method of treatment for improving the inhibition of gastric acid secretion which comprises administering to a host in need thereof an [comprising the] oral [administration of a] pharmaceutical formulation comprising a therapeutically effective amount of an acid labile H^+, K^+-ATPase inhibitor, wherein the method induces an extended blood plasma profile of the H^+, K^+-ATPase inhibitor, and the H^+, K^+-ATPase inhibitor is a compound of the formula I



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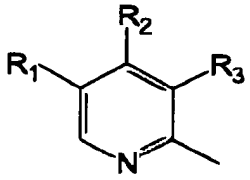

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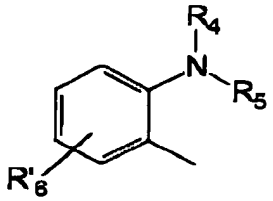

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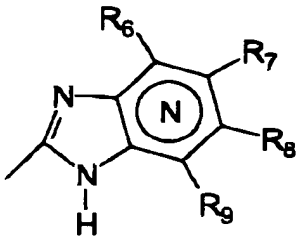

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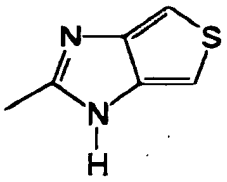

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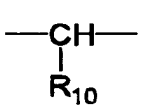

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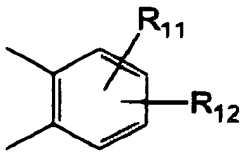


wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

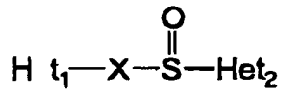
R_1, R_2 and R_3 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_6-R_9 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3; and

R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl.

18. (Thrice amended) A method of treatment for improving the inhibition of gastric acid secretion which comprises administering to a host in need thereof an [comprising the] oral [administration of a] pharmaceutical formulation comprising a therapeutically effective amount of an acid labile H^+, K^+-ATPase inhibitor, wherein the method induces an extended blood plasma profile of the H^+, K^+-ATPase inhibitor, and the H^+, K^+-ATPase inhibitor is a compound of the formula I



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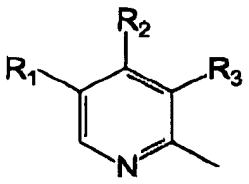

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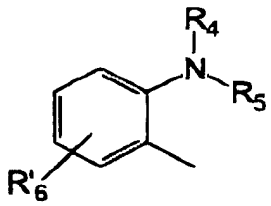

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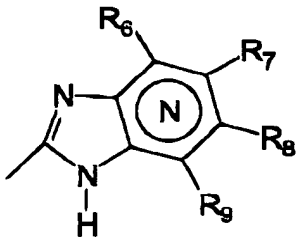

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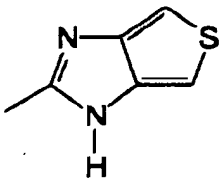

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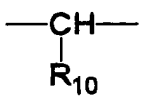

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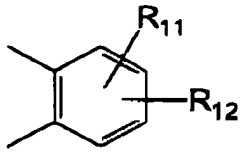

wherein

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R_1, R_2 and R_3 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

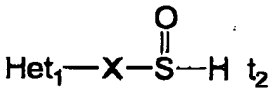
R_6-R_9 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3; and

R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl

with the proviso that the H^+, K^+-ATPase inhibitor is not pantoprazole.

26. (Twice amended) A method for improving the treatment of gastrointestinal disorders associated with excess acid secretion <u>which comprises administering to a host in need thereof an</u> [comprising the] oral [administration of a] pharmaceutical formulation comprising a therapeutically effective amount of an acid labile H^+, K^+-ATPase inhibitor, wherein the method induces an extended blood plasma profile of the H^+, K^+-ATPase inhibitor, and the H^+, K^+-ATPase inhibitor is a compound of the formula I



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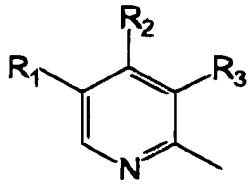

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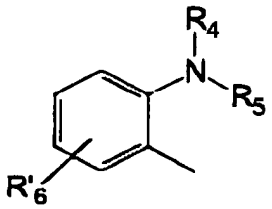

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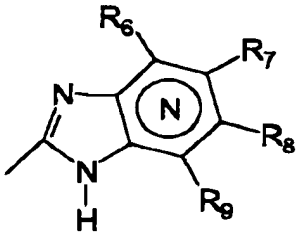

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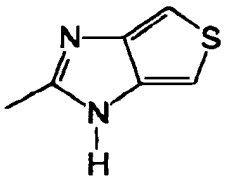

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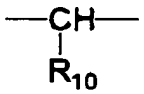

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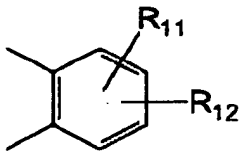

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R_{10} is hydrogen or forms an alkylene chain together with R_3; and

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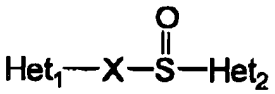
27. (Twice amended) A method for improving the treatment of gastrointestinal disorders associated with excess acid secretion <u>which comprises administering to host in need thereof an</u> [comprising the] oral [administration of a] pharmaceutical formulation comprising a therapeutically effective amount of an acid labile H^+, K^+-ATPase inhibitor, wherein the method induces an extended blood plasma profile of the H^+, K^+-ATPase inhibitor, and the H^+, K^+-ATPase inhibitor is a compound of the formula I



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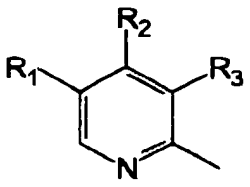

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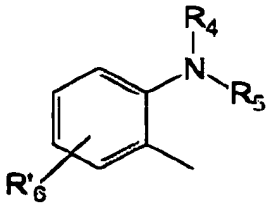
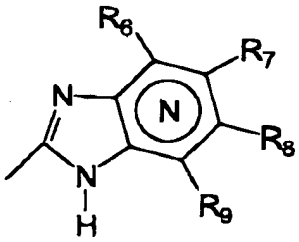


Het_2 is



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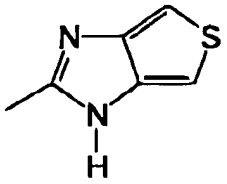
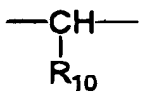


X =



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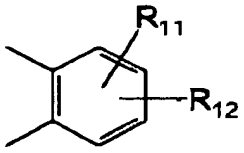

wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_6-R_9 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3; and

R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl,

with the proviso that the H^+, K^+-ATPase inhibitor is not pantoprazole.

CONCLUSION

The claim amendments and remarks set forth herein are fully responsive to the Office Action. It is respectfully submitted that claims 1-11, 18, 19 , 26 and 27 are in condition for allowance, which action is earnestly solicited.

Any additional fee in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: August 15, 2002

Respectfully submitted,

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